2. (AMENDED) A complex preparation for treatment of malignant neoplasms comprising:

alpha-fetoprotein (AFP),

a cytotoxic substance, and

a filler,

wherein a mass ratio of the AFP to the cytotoxic substance to the filler is 1:(60-100):(50-70).

3. (AMENDED) The complex preparation of claim 2, wherein the cytotoxic substance is a polyene antibiotic.

4. (AMENDED) The complex preparation of claim 2, wherein the filler is selected from the group consisting of dextran 100, dextran 70, dextran 40 and glucose.

8. (NEW) The complex preparation of claim 3, wherein the polyene antibiotic is amphotericin B.

9. (NEW) The complex preparation of claim 3, wherein the polyene antibiotic is nystatin.

REMARKS

Applicants have directed the undersigned attorney to submit the following response in connection with the office action mailed January 21, 2003. Applicants' response is set forth below:

> This Response is being filed in response to the Restriction and/or Election Requirement mailed on January 21, 2003. Applicants respond as follows:
>
> The Examiner has made the restriction requirement concerning invention I (claims 1 and 5-7) final under MPEP & 806.05(h).
>
> Applicants still disagree with this decision of the Examiner 's and therefore respectfully request the Examiner again to reconsider the said requirement basing on the following reasons, which unfortunately remained unsubmitted in the previous response.

In the first Office Action the Examiner has stated that inventions I and II are distinct from one another because alpha-fetoprotein (AFP) of invention II can be used in the materially different process of affinity purification of antibodies.

The claimed complex preparation of invention II is a three-component composition comprising AFP as one component thereof. AFP and amphotericin B (AB) together form a new complex with new properties. For example, AFP obtains a new electrophoretic mobility during gel-electrophoresis and another spectra of absorbance in UV-light. Possibly this reflects conformational changes in protein structure. At the same time, AFP in the complex preparation retains the ability to recognise cancer cells through own AFP receptor.

So, AFP-AB complex could not be used for affinity purification of antibodies to whole AFP because AFP in this complex differs in its structure and properties from native AFP. The result of the use of the three-component complex claimed for affinity purification of antibodies is therefore entirely unpredictable.

Applicants also disagree with different classification of inventions I and II and respectfully request the Examiner to reconsider the classification of invention II basing on the following:

The present classification of inventions I and II is as follows:

1) invention I is classified in class 514, subclass 12, corresponding according to US-to-IPC to class A61K,

2) invention II is now classified in class 530, subclass 350, corresponding according to US-to-IPC to class C07K, wherein a note is that the preparations for medicinal purposes are classified in class A61K.

The claimed complex preparation as a composition containing AFP as a component thereof is intended for treatment of malignant neoplasms and therefore belongs to the compositions for treating or curing abnormal and pathological conditions of the living body classified in class 514.

Therefore both the inventions should be classified in the same class 514. Applicants restrict claim 2, indicating the intended use (*for treatment of malignant neoplasms*) of the complex preparation.

On the ground of the explanations above Applicants state that inventions I and II are not distinct under MPEP §§ 806.05(h), but are related as product and process of use and therefore applicants respectfully request the Examiner to withdraw the requirement for restriction of invention I (reinstate claims 1 and 5-7) under 37 CFR 1.142(b) and 1.143.

Further the Examiner states that this application contains claims directed to the following patentably distinct species of the claimed invention:

Claim 2 is generic to a plurality of disclosed patentably distinct species comprising polyene antibiotics with different structures and functions wherein the antibiotics are (a) amphotericin B, (b) nystatin, both of claim 2.

Claim 2 is generic to a plurality of disclosed patentably distinct species comprising polysaccharides with different structures and functions wherein the polysaccharides are (a) polyglykine, (b) rheopolyglykine, (c) dextran, all of claims 4 and 6. It is noted that claims 4 and 6 appear to be identical.

Polyene macrolide antibiotics amphotericin B and nystatin of pending claim 3 are similar in structure (The Merck Index (An encyclopedia of chemicals, drugs and biologicals), 12th edition, 1996; amphotericin B, p. 99; nystatin, p. 1158) and with the same mechanism of action (Goodman & Gilman 's, The pharmacological basis of therapeutics (2001), 10th edition, pp. 1295-1298, 1310; H.P.Rang, M.M.Dale and J.M.Ritter, Pharmacology (1999), 4th edition, pp. 720-722; "Data for Biochemical Research", June, 1989, Clarendon

Press, Oxford, England. By Rex M.C.Dawson, Daphne C.Elliott,William H.Elliott, Kenneth M.Jones (Adv. Lip. Res. 14,127,1976); Holz, RW. 1974. The effects of the polyene antibiotics nystatin and amphotericin B on the lipid membranes. Ann. N. Y. Acad. Sci. 235: 469-479).

According to the records above both amphotericin B and nystatin interact with the sterols of cell membranes and cause the formation of pores or channels. The result is the permeability of the membrane, leading to leakage of cellular materials and cell death.

Basing on the similar structure and the same mechanism of action (the same function) the present polyene antibiotics amphotericin B and nystatin can not be considered as patentably distinct species, but they are obvious variants of the embodiment of the invention.

But taking into account the Examiner`s advice concerning an election of the species applicants elect the species amphotericin B.

Polysaccharides of pending claim 4 comprise dextrans of low molecular weight, i.e. dextran 100 (example 3), dextran 70 (polyglucin, the previous spelling ""polyglykine"" is wrong) and dextran 40 (rheopolyglucin).

The named dextrans are low molecular alpha-1,6-glycosidal connected alpha-D-glucoses with different chain length and therefore with different molecular weight.

The aim of the filler in the present complex preparation is to maintain the drug complex in an active form during lyophilization, drying and storage. The dextrans have been chosen because they provide the needable viscosity of the solution and so prevent the complex from aggregation at every stage of production and work. Glucose and dextrans are widely used for those purposes. Secondly, they are proved to be safe and can be used for clinical applications ("Review of clinical experience with standard clinical dextran in the United States", by B.W.Heynes, In "Conference on artificial colloidal agents", 27-28 Sept 1962,p.65-72; "The clinical use of Dextran solutions", by Amiel Segal,published

by Grune & Stratton, 1964, New York, London; European Pharmacopoeia Supplement 2000, 3 rd Edition; US Pharmacopoeia XXIV)

Those two reasons make the choice of fillers wide enough, so it is not restricted by glucose and dextrans, but the inventors have experience only with the named fillers.

Basing on the above applicants consider the said fillers, selected from the group consisting of dextran 100, dextran 70, dextran 40 and glucose, to be obvious variants of the embodiment of the invention and the generic claim covering all chosen fillers would be claim 2. Applicants respectfully hope that the Examiner will agree to this opinion.

Concerning an election of the invention applicants elect the invention covering claims 2-4 and 8.

Applicants would also like to point out that the reference to the closest method and to the closest complex preparation in [0008] and [0013] of the description of the invention as **U.S.** Pat. No. 2,065,307 must read patent **RU** 2,065,307.

Applicants respectfully submit that they have addressed the Examiner 's rejections.

CONCLUSION

In conjunction with the arguments above, Applicants believe that the pending claims are in condition for allowance. The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 10-0447, reference 53196-00002.

Docket No. 53196-00002
0968/P/JO

Respectfully submitted on Applicant's behalf
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Exhibit A

2. (AMENDED) A complex preparation for treatment of malignant neoplasms comprising:

alpha-fetoprotein (AFP),

a cytotoxic substance, and

a filler,

wherein a mass ratio of the AFP to the cytotoxic substance to the filler is [1-2] 1:(60-100):(50-70).

3. (AMENDED) The complex preparation of claim 2, wherein the cytotoxic substance [comprises] is a polyene antibiotic [, the polyene antibiotic being selected from the group consisting of amphotericin B and nystatin].

4. (AMENDED) The complex preparation of claim 2, wherein the filler [comprises at least one of a polysaccharide and glucose, the polysaccharide being selected from the group consisting of polyglykine, rheopolyglykine, and dextran] is selected from the group consisting of dextran 100, dextran 70, dextran 40 and glucose.

8. (NEW) The complex preparation of claim 3, wherein the polyene antibiotic is amphotericin B.

9. (NEW) The complex preparation of claim 3, wherein the polyene antibiotic is nystatin.